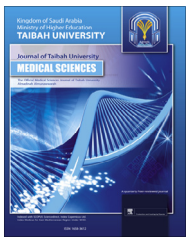
Journal of Taibah University Medical Sciences (2014) 9(2), 91–99

Taibah University

Journal of Taibah University Medical Sciences

www.sciencedirect.com



Review Article

Peripheral blood stem cells or bone marrow as the graft source for allogeneic hematopoietic cell transplantation?

Turki Alwasaidi, FRCPC [a,*] and Christopher Bredeson, FRCPC [a,b]

[a] *Ottawa Hospital Blood and Marrow Transplant Program, The Ottawa Hospital, Ottawa, Ontario, Canada*
[b] *Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada*

Received 14 June 2013; revised 12 November 2013; accepted 14 November 2013

الملخص

زراعة الخلايا الجذعية، أو ما يعرف أيضاً بزراعة نقي العظم، تستخدم لعلاج عدد من سرطانات الدم، وكذلك أمراض أخرى. ومصادر الخلايا الجذعية التي تستخدم من المتبرع ثلاثة وهي: نخاع العظم أو الخلايا الجذعية من الدم المحفزة بعامل تنشيط لنخاع العظم أو تجميع الخلايا الجذعية من الحبل السري مباشرة بعد الولادة. إن أول طريقة لتجميع الخلايا الجذعية من نخاع العظم تمت عن طريق السحب بإبر خاصة من عظم العرف الحرقفي تحت التخدير الكلي أو الموضعي للمتبرع. ولكن، أحدث اكتشاف طريقة تجميع الخلايا الجذعية من الدم المحفزة بعامل تنشيط لنخاع العظم، نقلة نوعية في مجال زراعة الخلايا الجذعية ونتائجها. فهذه الطريقة مريحة للمتبرع وتجنبه التعرض للتخدير والحاجة لدخول المستشفى. تختلف مكونات التطعيم المجمع من المتبرع الذي يحتوي على الخلايا الجذعية باختلاف المصدر، حيث أن كل مصدر له تأثير إيجابي أو سلبي على نتائج زراعته بالمُتبرع له. وبما أن زراعة الخلايا الجذعية المُجمعة من الحبل السري تعتبر في بداياتها، فإن عدد من الدراسات العلمية خلال السنوات الماضية ركز على مقارنة نتائج زراعة التطعيم من الخلايا الجذعية المحفزة من الدم بزراعة التطعيم من نقي العظم على المُتبرع له ومحاولة تحديد أيهما أفضل. من خلال هذه المراجعة البحثية ركزنا على مقارنة زراعة التطعيم من الخلايا الجذعية المحفزة من الدم بزراعة التطعيم من نقي العظم على المتبرعين وتأثيرها على النتائج السريرية للمُتبرع لهم بعد عملية الزراعة.

الكلمات المفتاحية: زراعة نقي العظم; داء الطعم حيال الثوي; زراعة مكونات الدم; متبرع قريب متطابق; الخلايا الجذعية من الدم المحفز; متبرع غير قريب

Abstract

Bone marrow (BM), granulocyte-colony stimulating factor mobilized peripheral blood stem cells (PBSC) and cord blood are the 3 sources of stem cells for allogeneic hematopoietic cell transplantation (HCT) that have been used to cure hematological malignancies and other disorders. Bone marrow obtained by repeated aspiration of the posterior iliac crests while the donor is under general or local anesthesia was the first source of hematopoietic stem cells. Introduction of PBSC as a source of stem cells resulted in important changes in transplant practices and outcomes. PBSC harvesting is more convenient for the donors with the advantage of avoiding anesthesia and hospitalization. There are differences in the composition of the graft sources that are reflected in different clinical outcomes both favorable and unfavorable. While the field of cord blood transplant is still in its infancy, there has been over the years many studies aimed at determining whether BM or PBSC grafts are superior. This review article summarizes our current knowledge on clinical outcomes between allogeneic transplants performed with peripheral blood stem cells (PBSC) and bone marrow (BM).

* Corresponding address: Blood Disease Centre, Ottawa Hospital Research Institute, 501 Smyth Road, Ottawa, ON K1H 8L6, Canada. Tel.: +1 (613) 737 8899x73904; fax: +1 (613) 737 8861.
E-mail: turkialwasaidi@hotmail.com (T. Alwasaidi)

Peer review under responsibility of Taibah University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jtumed.2013.11.004

Keywords: Bone marrow (BM); Graft-versus-host disease (GVHD); Hematopoietic cell transplant (HCT); Matched related donor (MRD); Peripheral blood stem cell (PBSC); Unrelated donor (URD)

Introduction

Allogeneic hematopoietic cell transplant (HCT) became feasible in the early 1960s after the identification and typing of Human Leukocyte Antigens (HLA), the major histocompatibility complex.[1–4] Allogeneic HCT is now a standard therapeutic approach to cure hematological malignancies and other disorders (Figure 1).[5]

The practice of allogeneic HCT has evolved over the past 4 decades and in general, outcomes have also improved.[6] Many factors in addition to the graft source affect post-transplant outcomes. In repeated studies over many years, important factors that influence post-transplant outcomes include patient age, performance status and medical comorbidities, diagnosis and disease stage, other characteristics of the disease and prior therapies, degree of HLA compatibility (related and unrelated donors), recipient and donor gender mismatch, GVHD prophylaxis, the intensity of the conditioning regimen, graft composition and cell (CD34+) dose and various aspects of supportive care.[1–4,7–17] Many of these variables are not modifiable while some can be improved by better patient selection. One aspect of the transplant, graft type, has received significant attention both in large observational registry studies as well as large randomized clinical trials. These studies have looked at the important clinical outcomes of morbidity, acute and chronic GVHD, disease control, survival and other important clinical outcomes (Table 1).[1]

Donating BM versus PBSC

In the beginning, all transplants used a bone marrow (BM) graft and all transplants were from matched sibling donors. BM was obtained by repeated aspiration of the posterior iliac crests with the donor under general or local anesthesia and was infused unmanipulated other than for red cell and possibly volume depletion. The discovery that granulocyte colony stimulating factor (G-CSF) could increase and mobilize the cells of interest from the bone marrow into the peripheral blood in large numbers led to a rapid adoption of this graft source. While initially applied in the autologous setting, it was not long until PBSC were applied in the allogeneic setting.[18–20] PBSC harvesting is more convenient for donors with the advantage of avoiding anesthesia and hospitalization and is associated with less morbidity.[21] Furthermore, G-CSF mobilized PBSC collection for allogeneic HCT is generally safe and well tolerated. The most common adverse event is bone pain in the axial skeleton, which is rarely severe (<1%).[21,22] There are other rare short-term adverse events associated with PBSC donation because of G-CSF administration (e.g. local reactions, severe headache, nausea, myalgia, splenic rupture), complications associated with placement of a CVC when peripheral access is inadequate (e.g. infection, bleeding, pneumothorax), and/or problems with leukapheresis (e.g. bleeding secondary to anticoagulation, hypocalcemia due to acid citrate dextrose [ACD] use).[21] A prospective randomized trial (RCT), that compared donation of BM versus G-CSF mobilized PBSC in HLA-matched sibling donors (MRD), showed BM donors had more fatigue and less energy than the PBPC donors post donation. BM donors but not PSBSC donors also had compromised quality of life (QoL) up to 1 month after donation.[22] Although theoretical concerns have been raised about G-CSF contributing to an increased risk of myeloid malignancies in healthy donors, an increase has not been seen in several small prospective and large retrospective studies of G-CSF treated donors.[21,23–25]

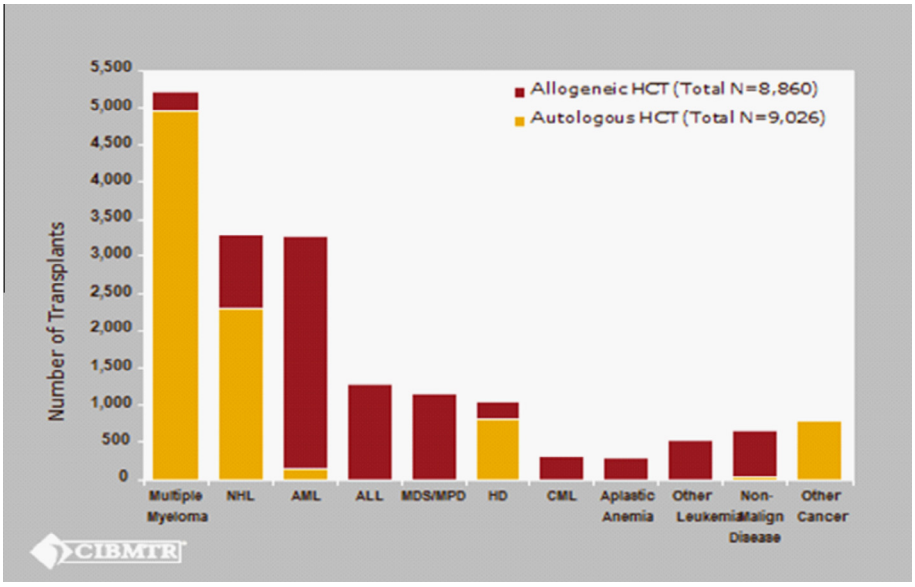


Figure 1: Indication of hematopoietic stem cell transplantation (HCT) in US, 2010 (CIBMTR registry).[2]

Table 1: Impact of PBSC graft compared BM graft on the outcomes of myeloablative conditioning allogeneic HCT.[*]

Disease	Age	Donor	Disease stage[#]	NRM	Relapse rate	aGVHD	cGVHD	DFS	OS
Hematological malignancies[++]	Adult	MRD	Early disease	=	↓	= or ↑	↑	= or ↑	=
			Late disease	=	↓	= or ↑	↑	↑	↑
		URD	Early & late disease	=	=	=	↑	=	=
	Children & adolescents (< 20 years)	MRD & URD	NA[$]	↑	=	=	↑	=	↓
Severe aplastic anemia (SAA)	All ages	MRD & URD	NA	↑	Equal risk of graft rejection	↑	↑	Equal mortality related to graft rejection	↓

Allogeneic HCT: allogeneic hematopoietic cell transplant, MRD: HLA-matched related donor, URD: HLA-matched unrelated donor, NRM: non-relapse mortality, aGVHD: acute graft versus host disease, cGVHD: chronic graft versus host disease, DFS: disease-free survival, OS: overall survival.
=: means equivalent outcomes or trials failed to show a difference.
↓: means decreased or inferior results with PBSC.
↑: means increased or superior results with PBSC.
[*] Other factors affecting the outcomes of allogeneic HCT include patient age, performance status and comorbidity, primary disease type, cytogenetics and stage, HLA compatibility (related and unrelated donors), gender mismatch, GVHD prophylaxis, conditioning regimens, and time of transplant.
[++] Hematological malignancies: AML, ALL, CML, MDS, CMML, and myelofibrosis.
[#] Late-stage disease was defined as CML > CP-1, AML > CR1, and MDS; RA-EB or RA-EB in transformation.
[$] NA: not available.

PBSC vs. BM in allogeneic HCT from HLA-matched related donor (MRD)

As stated above, the adoption of PBSC as a graft source for MRD allogeneic transplant was rapid and common. Registry data and surveys demonstrated increased use of PBSCs as the graft source for allogeneic hematopoietic cell transplants (HCT) that ranged between 50% and 80% (Figure 2), with much of the adoption predating definitive trial data.[5,26] Following several case series and registry studies suggesting benefits to PBSC, several randomized trials compared BM to PBSC in the setting of myeloablative conditioning regimen transplants from MRD. All trials reported PBSC graft associated with faster neutrophil and platelet engraftment compared to a BM graft in this setting.[27–33] The impact on treatment related mortality (TRM), relapse, GVHD and survival was more mixed. Bensinger reported the first RCT of 172 patients (12–55 years of age) with hematologic cancer.[27,28] Patients were randomized to receive BM or PBSC grafts following myeloablative (MA) conditioning regimens. This study showed no significant difference in incidence of grade > I acute GVHD at 100 days, chronic GVHD or 2 year overall survival (OS) between the groups. The 2 year disease free survival (DFS), however, was superior with PBSC compared to BM (66% vs. 45%; respectively, $P = 0.03$). A follow up report with a median follow up of 12.2 years confirmed superior DFS with PBSC compared with BM.[29] The estimated 10-year probability of relapse of primary disease was 20% with PBSC compared to 32% with BM ($P = 0.01$). Once again, however, the OS, incidence of chronic GVHD and the duration of systemic immunosuppressive therapy (IST) were similar in the groups. Quality of life data was not reported for surviving patients. A second RCT reported by Couban and colleagues included 228 patients with myeloid malignancies randomized to BM or PBSC from an HLA MRD.[30] All patients received busulfan and cyclophosphamide (BU/Cy) as pre-transplant conditioning therapy and cyclosporine (CSA) plus short course Methotrexate (MTX) as GVHD prophylaxis. Contrary to the Bensinger study, the 30 month OS was superior in the PBSC group compared to the BM group (68% vs. 60%; $P = 0.04$). The cumulative incidence of grades II to IV acute GVHD 100 days after transplantation, extensive chronic GVHD at 30 months and relapses were similar in both groups.

More recently the Stem Cell Trialists' Collaborative Group reported a meta-analysis using data from nine RCTs including the 2 outlined above.[31] The studies included 1111 adult patients with hematologic malignancies randomly assigned to receive a BM or PBSC graft from a MRD between 1990 and 2003. Results of the meta-analysis were again mixed and at times surprising. For example, non-relapse mortality (NRM) was similar between groups. PBSC transplants were associated with a significant increase of grade 3–4 acute GVHD but not grade 2–4 acute GVHD at 3 years compared to BM transplants (47% vs. 31% and 54% vs. 53%, respectively). More importantly, and in keeping with clinicians' impressions, the incidence of chronic GVHD at 3 years was higher with PBSC compared to BM (68% vs. 52%, respectively; $P < 0.000001$). A DFS and OS benefit with PBSC was only seen in patients with late-stage disease (41% vs. 27%; $P = 0.01$ and 46% vs. 31%; $P = 0.01$, for PBSC vs. BM, respectively). Late-stage disease was defined as chronic myelogenous leukemia more than chronic phase-1 (CML > CP-1), acute myeloid leukemia more than first complete remission (AML > CR1), myelodysplastic syndrome with excess blast or in transformation (RA-EB or RA-EB in transformation). A subsequent meta-analysis of 10 RCTs, not surprisingly, reported generally similar results for patients with hematologic malignancies

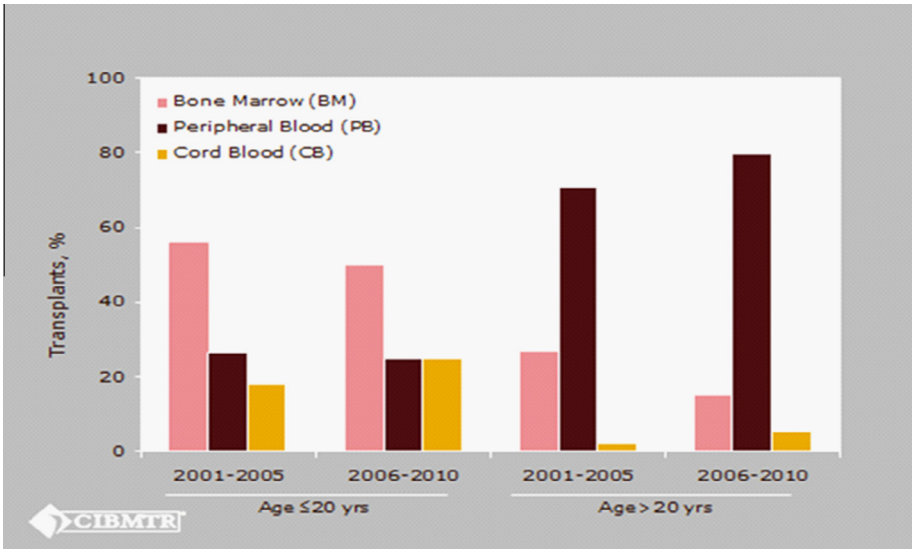


Figure 2: Graft source for allogeneic HCT by recipient age; between 2001 and 2010 (CIBMTR registry).[2]

(n = 1224) with the important exception that OS was not different between the groups.[32]

One caveat is that these trials included significant numbers of patients with chronic myeloid leukemia (CML); often in the range of 40–50% of the trial population. This disease has been demonstrated to be particularly amenable to the graft-versus-leukemia allograft effect and may have "over-estimated" the benefit of PBSC compared to BM based on higher numbers of T-lymphocytes in PBSC grafts. This limits to some degree the applicability of these results to present patient populations as allogeneic transplant for CML has essentially been replaced by oral tyrosine kinase inhibitors (TKIs) leaving patients with other, less immunologically sensitive myeloid malignancies to undergo allogeneic transplants.[34]

The interpretation and application of the above data favors the use of BM grafts for adult patients undergoing HLA matched related donor transplants for myeloid malignancies as survival is the same or very similar to PBSC transplants but with less chronic GVHD and potentially less severe acute GVHD.[27–32] For patients with advanced disease, PBSC may be chosen with hopes of obtaining an enhanced graft-versus-leukemia effect.[31]

PBSC vs. BM in allogeneic HCT from HLA-match-unrelated donor (URD)

In part based on convenience and the short-term advantages with PBSC seen in the related setting such as more rapid engraftment and potentially decreased early morbidity, the use of PBSC grafts for unrelated transplants dramatically increased over the past decade in the absence of comparative data. However, the results obtained with allogeneic HCT from HLA-identical siblings (MRD) may not necessarily extrapolate to the unrelated setting due in part to the higher risk of GVHD in the HCT from URD, even if the donor and recipient are fully HLA-matched.[1–3,33]

Multiple retrospective studies in the unrelated donor setting have demonstrated that PBSC grafts were associated with a higher incidence of chronic GVHD, similar relapse rates and no survival advantage compared to BM.[35–37] More recently, Anasetti and colleagues reported the outcomes of a large multicenter Phase III RCT (BMT CTN Protocol 0201) conducted by the North American BMT Clinical Trials Network.[33] This trial randomized 551 patients with hematologic malignancies to receive either PBSC (n = 273) or BM (n = 278) grafts from URDs. Forty-seven percent of the patients had AML and 28% had high-risk disease. PBSC recipients received significantly more $CD34^+$ cells compared to BM recipients (7.70 vs. 2.75×10^6/kg for PBSC vs. BM, respectively). The primary outcome in the trial, 2 year OS was not different between the groups. The incidence of acute GVHD and relapse rate were not significantly different between the groups. PBSC grafts compared to BM grafts were associated with less incidence of graft failure (3% vs. 9%; respectively, P = 0.002) and importantly, a higher incidence of chronic GVHD at 2 years (53% vs. 41%; respectively, P = 0.01). Moreover, extensive chronic GVHD was 48% with the PBSC grafts compared to 32% in BM grafts (P < 0.001). This study showed no survival differences according to graft source in planned subset analyses of patients with low and high risk malignancy or in those who received HLA-matched or mismatched grafts. Quality of life data is yet to be reported from this study. The absence of a survival advantage and a higher incidence of potentially debilitating chronic GVHD with PBSC grafts support the use of BM grafts for this patient population.[33,35–37]

PBSC vs. BM in allogeneic HCT using non-myeloablative (NMA) or reduced intensity conditioning (RIC)

The therapeutic effect of standard myeloablative allogeneic HCT is mediated by administration of high dose chemotherapy and/or radiation therapy (cytotoxic effect) and induction of an immune mediated graft versus tumor effect (immunotoxic effect).[38] The high-dose chemo-radiotherapy does not eradicate the malignancy in many patients and the therapeutic benefit of allogeneic HCT is dependent in varying degrees to the associated immune-mediated graft-versus-malignancy effect.[38,39] In the last ~15 years novel agents that are less toxic but very immune suppressive have led to the development of ablative but less toxic "reduced intensity" and the very low

intensity "non-myeloablative" conditioning regimens. Assignment to these categories is based on the duration of cytopenia and on the requirement for hematopoietic stem cell (HSC) support.[40] MA regimens cause irreversible cytopenia and HSC support is mandatory. NMA regimens cause minimal cytopenia, and can be given also without HSC support. RIC regimens do not fit criteria for MA or NMA regimens; they cause cytopenia of variable duration, and should be given with HSC support, although cytopenia may not be irreversible.

NMA and RIC allogeneic HCT have been reported to have better early tolerability but rely almost entirely on the graft-versus-tumor effect to cure patients.[41–49] They have yet to be shown to result in a definitive survival advantage in patients who would traditionally receive an ablative conditioning regimen.[8,50–53] They have however, allowed transplants to be offered to older and less robust patients.

There are limited quality data evaluating the impact of graft source in the setting of RIC or NMA transplants. One retrospective trial by Nagler and colleagues looked at the impact of the graft source (PBSCs vs. BM) in 602 patients with AML in complete remission who received RIC-allogeneic HCT from HLA-matched URD.[54] This study showed the PBSC grafts were associated with significantly higher incidence of acute GVHD and NRM, lower incidence of relapse but no statistically different leukemia free survival (LFS) when compared to BM graft.

The risk of graft failure is related to a complex mix of factors including prior therapy, disease status, conditioning regimen intensity, GVHD prophylaxis, donor type, degree of HLA match and graft source.[55–57] Early case series or single arm studies demonstrated a higher risk of graft rejection with some approaches to RIC or NMA transplantation and in patients with limited prior therapy.[58–60] Given the risk of graft failure with a BM graft in NMA and RIC-allogeneic HCT, many transplant centers prefer PBSC as the graft source, accepting the potential increase risk of chronic GVHD. However, in the absence of prospective comparative data the optimal graft source for NMA and RIC allogeneic HCT remains unknown.

PBSC vs. BM in allogeneic HCT for children and adolescents

PBSC allogeneic HCT are associated with inferior outcomes compared to BM transplants in children and adolescents.[61–63] Eapen and colleagues reported the outcomes of PBSC and BM transplants from MRD in children aged 8–20 years with acute leukemia from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry.[61] The risks of grade 2–4 acute GVHD were similar between the groups but the risk of chronic GVHD at 3 years was higher after the PBSC transplants compared to BM transplants (33% vs. 19%, respectively; $P = 0.001$). In addition, PBSC grafts were associated with higher TRM, treatment failure, and mortality. The 3-year OS in PBSC transplants was 48% compared to 58% with BM transplant ($P = 0.01$). Similarly, a recent retrospective study showed increased chronic GVHD and worse survival with PBSC grafts compared to BM grafts for MRD allogeneic HCT in Japanese children with acute leukemia.[62] The 5-year OS was significantly lower after PBSC transplants compared to BM transplants for ALL (42.4% vs. 63.7%, $P = 0.003$) and AML (49.8% vs. 71.8%, $P = 0.016$).

PBSC vs. BM in allogeneic HCT for patients with aplastic anemia

Severe aplastic anemia (SAA) is an immune-mediated disorder; T lymphocytes inhibit or destroy hematopoietic progenitor cells resulting in marrow failure.[64] Treatment options include immune suppressive therapy (IST) with ATG and cyclosporine and allogeneic HCT depending on the patient's age and matched donor availability. When an HLA-matched sibling is lacking or the patient is >40 years old, IST is the recommended first-line treatment with HCT reserved for those patients who fail IST.[64,65] Multiple studies have demonstrated that bone marrow is preferred as the graft source for patients with aplastic anemia as PBSC grafts are associated with worse transplant outcomes compared to BM grafts.[63–68]

For example, Schrezenmeier reported combined CIBMTR and European Bone Marrow Transplant (EBMT) data that showed a higher incidence of chronic GVHD and higher mortality with PBSC compared to BM grafts in SAA patients younger than 20 years of age receiving a first allogeneic HCT from HLA-MRD (relative risk (RR), 2.82; $P = 0.002$ and RR, 2.04; $P = 0.024$, respectively).[63] In younger patients, the 5-year OS was 73% and 85% after PBSC and BM transplants, respectively. In this study, chronic GVHD and overall mortality rates were similar after PBSC and BM transplants in patients older than 20 years. Higher chronic GVHD after PBPC transplants in younger patients likely contributed to the excess mortality. Similarly, Bacigalupo reported a large registry study of combined CIBMTR and EBMT data analyzing outcomes of MRD allogeneic transplants for SAA.[66] This study compared outcomes of patients with SAA who received a first HCT from a HLA-MRD with either a BM ($n = 1163$) or PBSC ($n = 723$) graft. The incidence of acute and chronic GVHD was higher with PBSC grafts. More importantly, survival was inferior with PBSC grafts compared to BM grafts in patients younger than 20 (76% vs. 90%; respectively, $P < 0.00001$) as well as in patients older than 20 years (64% vs. 74%; respectively, $P = 0.001$). Chu and colleagues from CIBMTR published similar findings of higher rates of acute and chronic GVHD in PBSC recipients compared to BM recipients in patients who underwent an HLA-MRD transplant for SAA.[67]

In terms of HLA-matched URD allogeneic transplant for SAA, Eapen and colleagues reported higher mortality, independent of age, with PBSC grafts compared to BM grafts in 296 patients with SAA that included both pediatric and adult patients.[68] In this retrospective study, grade 2–4 acute GVHD was higher with PBSC grafts compared to BM grafts. However, hematopoietic recovery and chronic GVHD risks were not significantly different between the groups.

In summary, for SAA in both children and adults whether from an HLA-MRD or MUD, bone marrow is the preferred graft source.

Ongoing graft source research

One approach to try and achieve the benefits of both BM grafts (lower chronic GVHD) and PBSC grafts (faster engraftment and perhaps enhanced GVL) has been the use of HSC collected from a bone marrow after the donor has been given G-CSF to "prime" the bone marrow (G-BM).[69–71] A

large Canadian trial comparing G-BM to PBSC in related donor transplants has recently completed accrual and should provide important comparative data in the near term.

Plerixafor is a recently approved drug used to mobilize HSC from the marrow in the autologous transplant setting. Plerixafor is a new HSC mobilizing drug that antagonizes the binding of the chemokine stromal-cell-derived factor-1alpha (SDF-1alpha) to CXC chemokine receptor 4 (CXCR4).[72] This drug is able to mobilize HSC when G-CSF or chemotherapy + G-CSF have failed and pre-clinical studies suggest that it may produce a superior stem cell graft to G-CSF alone. Plerixafor when used in conjunction with G-CSF as a PBSC mobilization agent has allowed more patients with multiple myeloma, non-Hodgkin's lymphoma, and Hodgkin's disease to mobilize sufficient HSC to proceed to autologous HCT.[73–76] Plerixafor is now under investigation for HSC collection from healthy donors for allogeneic HCT. Also of interest, there is an ongoing phase I/II study to test the safety and efficacy of post-transplant administration of plerixafor to enhance donor hematopoietic cell engraftment after myeloablative allogeneic HCT (NCT01280955).

Summary and conclusion

Many factors besides the graft source affect the short-term and long-term outcomes of allogeneic HCT including patient's age, performance status and medical comorbidities, diagnosis and disease status, donor type, degree of HLA match, gender mismatch, GVHD prophylaxis, intensity of the conditioning regimens, graft composition and cell (CD34+) dose.[1–4,7–17] In HLA-MRD and URD with myeloablative conditioning regimens, bone marrow is the preferred graft source as it is associated with similar survival but less risk for chronic GVHD compared to PBSC.[31–33] With advanced or poor-risk disease, PBSC may offer the potential of improved DFS and OS.[27,31]

In some settings, allogeneic HCT for hematological malignancies using NMA and RIC results in reduced early treatment related morbidity and treatment related mortality compared to standard myeloablative conditioning without a survival advantage or difference in the incidence of chronic GVHD.[8,50–53] They have, however, extended the transplant option to older and more medically complex patients. In general, PBSCs for RIC-allogeneic HCT are associated with a lower risk of graft failure compared to BM graft.[54–60] Although general clinical practice favors PBSC for NMA and RIC allogeneic transplants, this remains a preference in the absence of prospective comparative data.

Bone marrow grafts are preferred for allogeneic HCT in children and adolescents with hematologic malignancies.[61,62] Finally, patients with SAA of all ages undergoing an allogeneic HCT should receive bone marrow grafts.[63–68]

Future research through registry studies and clinical trials will continue to explore differences between these graft sources. Two areas of interest remain trying to find the best of both graft types, perhaps with G-CSF primed BM and ways to facilitate the donor process perhaps with the use of novel mobilizing agents such as plerixafor.

Authorship

Opinions and conclusions or recommendations expressed herein are those of the authors. Authors are responsible for data acquisition and final approval of the manuscript.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

Acknowledgments

The authors thank Dr. Lothar Huebsch for thoroughly editing of this review article. Also, the authors thank Taibah University, Saudi Arabia, for funding a scholarship for Dr. T. Alwasaidi, through the Saudi Arabian Cultural Bureau in Canada.

References

1. Copelan EA. Hematopoietic stem-cell transplantation. **N Engl J Med 2006**; 354(17): 1813–1826.
2. Flomenberg N, Baxter-Lowe LA, Confer D, et al. Impact of HLA class I and class II high-resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplantation outcome. **Blood 2004**; 104(7): 1923–1930.
3. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor–recipient HLA matching contributes to the success of unrelated donor marrow transplantation. **Blood 2007**; 110(13): 4576–4583.
4. Saber W, Opie S, Rizzo JD, Zhang MJ, Horowitz MM, Schriber J. Outcomes after matched unrelated donor versus identical sibling hematopoietic cell transplantation in adults with acute myelogenous leukemia. **Blood 2012**; 119(17): 3908–3916.
5. Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides; **2012**. Available at: http://www.cibmtr.org.
6. Hahn T, McCarthy Jr PL, Hassebroek A, Bredeson C, et al. Significant improvement in survival after allogeneic hematopoietic cell transplantation during a period of significantly increased use, older recipient age, and use of unrelated donors. **J Clin Oncol 2013**; 31(19): 2437–2449.
7. Bensinger WStem Cell Trialists' Collaborative Group. Individual patient data meta-analysis of allogeneic peripheral blood stem cell transplant vs. bone marrow transplant in the management of hematological malignancies: indirect assessment of the effect of day 11 methotrexate administration. **Bone Marrow Transplant 2006**; 38(8): 539–546.
8. Couriel DR, Saliba RM, Giralt S, et al. Acute and chronic graft-versus-host disease after ablative and nonmyeloablative conditioning for allogeneic hematopoietic transplantation. **Biol Blood Marrow Transplant 2004**; 10(3): 178–185.
9. Brandwein JM, Geddes M, Kassis J, Kew AK, et al. Treatment of older patients with acute myeloid leukemia (AML): a Canadian consensus. **Am J Blood Res 2013**; 3(2): 141–164.
10. Finke J, Schmoor C, Bethge WA, Ottinger HD, et al. Prognostic factors affecting outcome after allogeneic transplantation for hematological malignancies from unrelated donors: results from a randomized trial. **Biol Blood Marrow Transplant 2012**; 18(11): 1716–1726.
11. Messina C, Faraci M, de Fazio V, Dini G, Calò MP, Calore EEBMT Paediatric Working Party. Prevention and treatment of acute GVHD. **Bone Marrow Transplant 2008**; 41(Suppl. 2): S65–S70.
12. Pulsipher MA, Chitphakdithai P, Logan BR, Leitman SF, et al. Donor, recipient, and transplant characteristics as risk factors after unrelated donor PBSC transplantation: beneficial effects of higher CD34+ cell dose. **Blood 2009**; 114(13): 2606–2616.
13. Bacigalupo A, Lamparelli T, Bruzzi P, et al. Antithymocyte globulin for graft-versus-host disease prophylaxis in transplants from unrelated donors: 2 randomized studies from Gruppo

Italiano Trapianti Midollo Osseo (GITMO). **Blood 2001**; 98(10): 2942–2947.
14. Bacigalupo A, Lamparelli T, Barisione G, Bruzzi P, et al. Thymoglobulin prevents chronic graft-versus-host disease, chronic lung dysfunction, and late transplant-related mortality: long-term follow-up of a randomized trial in patients undergoing unrelated donor transplantation. **Biol Blood Marrow Transplant 2006**; 12(5): 560–565.
15. Finke J, Bethge WA, Schmoor C, Ottinger HD, et al. Standard graft-versus-host disease prophylaxis with or without anti-T-cell globulin in haematopoietic cell transplantation from matched unrelated donors: a randomised, open-label, multicentre phase 3 trial. **Lancet Oncol 2009**; 10(9): 855–864.
16. Socié G, Schmoor C, Bethge WA, Ottinger HD, et al. Chronic graft-versus-host disease: long-term results from a randomized trial on graft-versus-host disease prophylaxis with or without anti-T-cell globulin ATG-Fresenius. **Blood 2011**; 117(23): 6375–6382.
17. Russell JA, Turner AR, Larratt L, et al. Adult recipients of matched related donor blood cell transplants given myeloablative regimens including pretransplant antithymocyte globulin have lower mortality related to graft-versus-host disease: a matched pair analysis. **Biol Blood Marrow Transplant 2007**; 13(3): 299–306.
18. Kessinger A, Smith DM, Standjord SE, Landmark JD, Dooley P, Law P, Coccia PF, Warkentin PI, Weisenburg DD, Armitage JO. Allogeneic transplantation of blood-derived, T cell-depleted hematopoietic stem cells after myeloablative treatment in a patient with acute lymphoblastic leukemia. **Bone Marrow Transplant 1989**; 4(6): 643–646.
19. Russell NH, Hunter A, Rogers S, Hanley J, Anderson D. Peripheral blood stem cells as an alternative to marrow for allogeneic transplantation. **Lancet 1993**; 341: 1482.
20. Dreger P, Hafurlach T, Eckstein V, Jacues S, Suttorp M, Loffler W, Millller-Richmoltz W, Schmitz N. G-CSF-mobilized peripheral blood progenitor cells for allogeneic transplantation: safety, kinetics of mobilization, and composition of the graft. **Br J Haematol 1994**; 87: 609.
21. Pulsipher MA, Chitphakdithai P, Miller JP, Logan BR, et al. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. **Blood 2009**; 113(15): 3604–3611.
22. Bredeson C, Leger C, Couban S, Simpson D, Huebsch L, et al. An evaluation of the donor experience in the Canadian multicenter randomized trial of bone marrow versus peripheral blood allografting. **Biol Blood Marrow Transplant 2004**; 10(6): 405–414.
23. Anderlini P, Chan FA, Champlin RE, Korbling M, Strom SS. Long-term follow-up of normal peripheral blood progenitor cell donors treated with filgrastim: no evidence of increased risk of leukemia development. **Bone Marrow Transplant 2002**; 30: 661–663.
24. Sakamaki S, Matsunaga T, Hirayama Y, Kuga T, Niitsu Y. Haematological study of healthy volunteers 5 years after G-CSF. **Lancet 1995**; 346: 1432–1433.
25. Cavallaro AM, Lilleby K, Majolino I, et al. Three to six year follow-up of normal donors who received recombinant human granulocyte colony-stimulating factor. **Bone Marrow Transplant 2000**; 25: 85–89.
26. Gratwohl A, Baldomero H, Horisberger B, et al. Current trends in hematopoietic stem cell transplantation in Europe. **Blood 2002**; 100: 2374–2386.
27. Bensinger WI, Martin PJ, Storer B, et al. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. **N Engl J Med 2001**; 344(3): 175–181.
28. Flowers ME, Parker PM, Johnston LJ, et al. Comparison of chronic graft-versus-host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. **Blood 2002**; 100(2): 415–419.
29. Mielcarek M, Storer B, Martin PJ, Forman SJ, et al. Long-term outcomes after transplantation of HLA-identical related G-CSF-mobilized peripheral blood mononuclear cells versus bone marrow. **Blood 2012**; 119(11): 2675–2678.
30. Couban S, Simpson DR, Barnett MJ, Bredeson C, Hubesch L, et al. A randomized multicenter comparison of bone marrow and peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. **Blood 2002**; 100(5): 1525–1531.
31. Bensinger W et alStem Cell Trialists' Collaborative Group. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. **J Clin Oncol 2005**; 23(22): 5074–5087.
32. Zhang H, Chen J, Que W. Allogeneic peripheral blood stem cell and bone marrow transplantation for hematologic malignancies: meta-analysis of randomized controlled trials. **Leuk Res 2012**; 36 (4): 431–437.
33. Anasetti C, Logan BR, Lee SJ, Waller EK, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. **N Engl J Med 2012**; 367(16): 1487–1496.
34. Cortes J, Kantarjian H. How I treat newly diagnosed chronic phase CML. **Blood 2012**; 120(7): 1390–1397.
35. Remberger M, Beelen DW, Fauser A, Basara N, Basu O, Ringdén O. Increased risk of extensive chronic graft-versus-host disease after allogeneic peripheral blood stem cell transplantation using unrelated donors. **Blood 2005**; 105(2): 548–551.
36. Garderet L, Labopin M, Gorin NC, et al. Patients with acute lymphoblastic leukaemia allografted with a matched unrelated donor may have a lower survival with a peripheral blood stem cell graft compared to bone marrow. **Bone Marrow Transplant 2003**; 31(1): 23–29.
37. Eapen M, Logan BR, Confer DL, Haagenson M, Wagner JE, et al. Peripheral blood grafts from unrelated donors are associated with increased acute and chronic graft-versus-host disease without improved survival. **Biol Blood Marrow Transplant 2007**; 13(12): 1461–1468.
38. Champlin R, Khouri I, Shimoni A, Gajewski J, et al. Harnessing graft-versus-malignancy: non-myeloablative preparative regimens for allogeneic haematopoietic transplantation, an evolving strategy for adoptive immunotherapy. **Br J Haematol 2000**; 111(1): 18–29.
39. Shimoni A, Nagler A. Optimizing the conditioning regimen for allogeneic stem-cell transplantation in acute myeloid leukemia; dose intensity is still in need. **Best Pract Res Clin Haematol 2011**; 24(3): 369–379.
40. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, et al. Defining the intensity of conditioning regimens: working definitions. **Biol Blood Marrow Transplant 2009**; 15(12): 1628–1633.
41. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. **Blood 2001**; 97: 3390–3400.
42. Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. **Blood 1998**; 91: 756–763.
43. Sandmaier BM, Maloney DG, Gooley T, et al. Nonmyeloablative hematopoietic stem cell transplants (HSCT) from HLA-matched related donors for patients with hematologic malignancies: clinical results of a TBI-based conditioning regimen abstract. **Blood 2001**; 98(part 1): 742.
44. Maris M, Niederwieser D, Sandmaier B, et al. Nonmyeloablative hematopoietic stem cell transplants (HSCT) using 10/10 HLA antigen matched unrelated donors (URDs) for patients with advanced hematologic malignancies ineligible for conventional HSCT abstract. **Blood 2001**; 98(part 1): 858.

45. Georges GE, Maris M, Sandmaier BM, Malone DG, Feinstein L, et al. Related and unrelated nonmyeloablative hematopoietic stem cell transplantation for malignant diseases abstract. **Int J Hematol 2002**; 76(Suppl. 1): 184–189.
46. Khouri IF, Keating M, Körbling M, et al. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. **J Clin Oncol 1998**; 16: 2817–2824.
47. Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. **Blood 2001**; 97: 631–637.
48. Giralt S, Estey E, Albitar M, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. **Blood 1997**; 89: 4531–4536.
49. Mielcarek M, Sandmaier BM, Maloney DG, et al. Nonmyeloablative hematopoietic cell transplantation: status quo and future perspectives. **J Clin Immunol 2002**; 22: 70–74.
50. Bornhäuser M, Kienast J, Trenschel R, Burchert A, et al. Reduced-intensity conditioning versus standard conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: a prospective, open-label randomised phase 3 trial. **Lancet Oncol 2012**; 13(10): 1035–1044.
51. Jagasia M, Arora M, Flowers ME, Chao NJ, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. **Blood 2012**; 119(1): 296–307.
52. Sorror ML, Maris MB, Storer B, et al. Comparing morbidity and mortality of HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative and myeloablative conditioning: influence of pretransplantation comorbidities. **Blood 2004**; 104(4): 961–968.
53. Mielcarek M, Martin PJ, Leisenring W, et al. Graft-versus-host disease after nonmyeloablative versus conventional hematopoietic stem cell transplantation. **Blood 2003**; 102(2): 756–762.
54. Nagler A, Labopin M, Shimoni A, Niederwieser D, et al. Mobilized peripheral blood stem cells compared with bone marrow as the stem cell source for unrelated donor allogeneic transplantation with reduced-intensity conditioning in patients with acute myeloid leukemia in complete remission: an analysis from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. **Biol Blood Marrow Transplant 2012**; 18(9): 1422–1429.
55. Olsson R, Remberger M, Schaffer M, Berggren DM, Svahn BM, Mattsson J, Ringden O. Graft failure in the modern era of allogeneic hematopoietic SCT. **Bone Marrow Transplant 2013**; 48 (4): 537–543.
56. Passweg JR, Zhang MJ, Rocha V, Kan F, Champlin RE, Isola LM, et al. Donor characteristics affecting graft failure, graft-versus-host disease, and survival after unrelated donor transplantation with reduced-intensity conditioning for hematologic malignancies. **Biol Blood Marrow Transplant 2011**; 17(12): 1869–1873.
57. Le Blanc K, Remberger M, Uzunel M, Mattsson J, et al. A comparison of nonmyeloablative and reduced-intensity conditioning for allogeneic stem-cell transplantation. **Transplantation 2004**; 78(7): 1014–1020.
58. Maris MB, Niederwieser D, Sandmaier BM, Storer B, et al. HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative conditioning for patients with hematologic malignancies. **Blood 2003**; 102(6): 2021–2030.
59. Maris MB, Sandmaier BM, Storer BE, Maloney DG, et al. Unrelated donor granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cell transplantation after nonmyeloablative conditioning: the effect of postgrafting mycophenolate mofetil dosing. **Biol Blood Marrow Transplant 2006**; 12(4): 454–465.
60. Nakamae Hirohisa, Storer Barry E, Storb Rainer, et al. Low-dose total body irradiation and fludarabine conditioning for HLA-class I mismatched donor stem cell transplantation and immunological recovery in patients with hematological malignancies: a multi-center trial. **Biol Blood Marrow Transplant 2010**; 16(3): 384.
61. Eapen M, Horowitz MM, Klein JP, et al. Higher mortality after allogeneic peripheral-blood transplantation compared with bone marrow in children and adolescents: the Histocompatibility and Alternate Stem Cell Source Working Committee of the International Bone Marrow Transplant Registry. **J Clin Oncol 2004**; 22 (24): 4872–4880.
62. Shinzato A, Tabuchi K, Atsuta Y, Inoue M, Inagaki J, et al. PBSCT is associated with poorer survival and increased chronic GvHD than BMT in Japanese paediatric patients with acute leukaemia and an HLA-matched sibling donor. **Pediatr Blood Cancer 2013**; 60(9): 1513–1519.
63. Schrezenmeier H, Passweg JR, Marsh JC, Bacigalupo A, Bredeson CN, et al. Worse outcomes and more chronic GVHD with peripheral blood progenitor cells than bone marrow in HLA-matched sibling donor transplants for young patients with severe acquired aplastic anemia. **Blood 2007**; 110(4): 1397–1400.
64. Young NS, Calado RT, Scheinburg P. Current concepts in the pathophysiology and treatment of aplastic anemia. **Blood 2006**; 108(8): 2509–2519.
65. Marsh JCW, Ball SE, Cavenagh J, et al. Guidelines for the diagnosis and management of aplastic anemia. **Br J Haematol 2009**; 147(1): 43–70.
66. Bacigalupo A, Socié G, Schrezenmeier H, Tichelli A, Locasciulli M, Fuehrer M, et alAplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT). Bone marrow versus peripheral blood as the stem cell source for sibling transplants in acquired aplastic anemia: survival advantage for bone marrow in all age groups. **Haematologica 2012**; 97(8): 1142–1148.
67. Chu R, Brazauskas R, Kan F, Bashey A, Bredeson C, et al. Comparison of outcomes after transplantation of G-CSF stimulated bone marrow grafts versus bone marrow or peripheral blood grafts from HLA-matched sibling donors for patients with severe aplastic anemia. **Biol Blood Marrow Transplant 2011**; 17(7): 1018–1024.
68. Eapen M, Le Rademacher J, Antin JH, Champlin RE, et al. Effect of stem cell source on outcomes after unrelated donor transplantation in severe aplastic anemia. **Blood 2011**; 118(9): 2618–2621.
69. Morton J, Hutchins C, Durrant S. Granulocyte-colony-stimulating factor (G-CSF)-primed allogeneic bone marrow: significantly less graft-versus-host disease and comparable engraftment to G-CSF-mobilized peripheral blood stem cells. **Blood 2001**; 98(12): 3186–3191.
70. Styczyński J, Debski R, Krenska A, Wysocki M. G-CSF-primed bone marrow as a stem-cell source for allogeneic bone marrow transplantation in children. **Med Wieku Rozwoj 2008**; 12(4 Pt 2): 1112–1116.
71. Frangoul H, Nemecek ER, Billheimer D, Pulsipher MA, et al. A prospective study of G-CSF primed bone marrow as a stem-cell source for allogeneic bone marrow transplantation in children: a Pediatric Blood and Marrow Transplant Consortium (PBMTC) study. **Blood 2007**; 110(13): 4584–4587.
72. Kessans MR, Gatesman ML, Kockler DR. Plerixafor: a peripheral blood stem cell mobilizer. **Pharmacotherapy 2010**; 30(5): 485–492.
73. DiPersio JF, Micallef IN, Stiff PJ, Bolwell BJ, et al. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. **J Clin Oncol 2009**; 27(28): 4767–4773.

74. Micallef IN, Stiff PJ, DiPersio JF, Maziarz RT, et al. Successful stem cell remobilization using plerixafor (mozobil) plus granulocyte colony-stimulating factor in patients with non-hodgkin lymphoma: results from the plerixafor NHL phase 3 study rescue protocol. **Biol Blood Marrow Transplant 2009**; 15 (12): 1578–1586.
75. DiPersio JF, Stadtmauer EA, Nademanee A, Micallef IN, et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. **Blood 2009**; 113(23): 5720–5726.
76. Nademanee AP, DiPersio JF, Maziarz RT, et al. Plerixafor plus granulocyte colony-stimulating factor versus placebo plus granulocyte colony-stimulating factor for mobilization of CD34 (+) hematopoietic stem cells in patients with multiple myeloma and low peripheral blood CD34 (+) cell count: results of a subset analysis of a randomized trial. **Biol Blood Marrow Transplant 2012**; 18(10): 1564–1572.